UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,006	03/22/2004	Ashley J. Birkett	91644	1250

24628 7590 06/20/2006

WELSH & KATZ, LTD
120 S RIVERSIDE PLAZA
22ND FLOOR
CHICAGO, IL 60606

EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 06/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,006	BIRKETT, ASHLEY J.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *79-97 and 110-115* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *79-97 and 110-115* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the Patent and Trademark Office has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Bo Peng, Art Unit 1648.

2. This Office Action is in response to the amendment filed 7 April 2005. Claims 1-78 and 98-109 are cancelled. Claims 79, 80 and 82 are amended; Claims 79-97 and 110-115 are pending are under consideration.

3. The rejections of claims 79-97 and 110-115 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **are withdrawn** in view of Applicant's amendment and arguments.

4. The rejection of claims 79-97 and 110-115 under 35 U.S.C. § 112, first paragraph **is withdrawn** in view of Applicant's amendment.

5. The rejections of claims 1 and 11 under 35 U.S.C 102(b) as being anticipated by Zlotnick (1997) **are withdrawn** in view of Applicant's amendment.

6. The rejection of claim 79 and 80 under 35 U.S.C 102(b) as being anticipated by Yoshikawa (1993) **is withdrawn** in view of Applicant's amendment.

7. The rejection of claim 79 and 80 under 35 U.S.C 102(b) as being anticipated by Zlotnick (1997) **is withdrawn** in view of Applicant's amendment.

8. The rejection of claim 79, 80, 87, 110, 111 and 113-115 under 35 U.S.C 102(b) as being anticipated by Stahl (1989) **is withdrawn** in view of Applicant's amendment.

9. The rejections of claims 79, 80, 82-97, 110, 111 and 113-115 under 35 U.S.C. §103, as being obvious over Ireland (US Patent 5,990,085) in view of Zlotnick *et al.* (1997) **are maintained**.

10. Applicant argues that Examiner mischaracterized the instant claim 78 (b) and rejection should be withdrawn, as should Ireland as a reference against the claims.

11. Applicant's argument is not convincing for the following reasons: As explained in the previous Office action, Examiner did not use Ireland as a 102 reference since Examiner could not determine where cysteines(s) is located in C-terminal of HBc molecule from the claim language of claim 78(b). To demonstrate the pertinent prior art regarding to the effect of Cys on C-terminal truncated HBcAg, Examiner has further cited Zlotnick's reference, which teaches adding a c-terminal cysteine residue to achieve a stabilizing effect. Therefore, Ireland as a 103 reference in view of Zlotnick were applied properly.

12. The previous Office action pointed out that Zlotnick et al. teaches adding a c-terminal cysteine residue to achieve a stabilizing effect (See pgs. 9556 and 9558). Zlotnick's HBc chimera contained the HBc sequence from position 135-149 with a terminal cysteine at position 150, thus

meeting the dual limitations of a chimer that contains (1) a sequence of at least 5 amino acid residues from HBC position 135 to the HBC C-terminus and one to ten cysteines residues toward the C-terminus of the molecule from the C-terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C- terminal cysteine residue(s)]. Zlotnick clearly demonstrates that the c-terminal particles are more stable than are particles formed from an otherwise identical HBC chimer that lacks said C-terminal cysteine residue(s) (see page 9558, col. 1, first and second full paragraphs).

13. One of ordinary skill in the art would have been motivated to combine the teachings of the '085 patent teaching HBc as an epitope carrier with that of Zlotnick because it was well known that HBc chimeras with c-terminal deletions, while still capable of self-assembly, were less stable than their full-length counterparts and that by adding back amino acid residues to these c-terminal deletion one could achieve a more stable chimera, while Zlotnick teaches that the addition of a cysteine residue to an HBc c-terminal truncation results in enhanced stability. One of ordinary skill in the art would have expected to achieve a more stable HBc chimera with a c-terminal truncation by the addition of a cysteine residue because Zlotnick teaches that the addition of a cysteine to the c-terminal of an HBc molecule with a c-terminal truncation results in enhanced stability.

14. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

15. The rejections of claims 79-97 under 35 U.S.C. §103, as being obvious over Zlotnick *et al.* (1997) and further in view of Pumpens (1995) **are maintained**.

16. Applicant argues that the rejection should be withdrawn because (1) the Office action misused Tables 1 of Pumpens' reference, because Table 1 of Pumpens' paper relates to "full length" HBc, but the instant invention is a C-terminal deleted HBc (remarks, 3rd paragraph, p23); (2) Pumpens' statement that foreign insertions exert a stabilizing effect on chimeric HBcΔ is not legitimate because it is based on unpublished results (remarks, 2nd paragraph, p24); and (3) Zlotnick's reference does not apply to the instant claims because it says nothing about the effect of a C-terminal cysteine on a truncated HBc molecule that has its internal cysteines nor such a molecule that has an inserted sequence" (remarks, 1st paragraph, p25).

17. Applicant's arguments are considered but found not persuasive for following reasons:

18. First at all, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The suggestion to combine or modify the teaching of the prior art can be established either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). To establish a *prima facie* case of obviousness, the Board must, *inter alia*, show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

19. In response to Applicant's argument (1), specifically, that the Office action misused Table 1 of Pumpens' reference, the Office action has not misused Pumpens' reference. In fact, the

Office action has recited Table 1 to show that Pumpens teaches "chimers contain an HBC sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule that include a peptide-bonded heterologous epitope (Table 1)", which is one of limitations of the instant claims. The Examiner has clearly pointed out in the previous Office action that "Pumpens discloses that HBc chimeras with c-terminal truncated are capable of self-assembly and do not bind or 'pack' nucleic acid (page 67, col.1). Therefore, the Pumpens' reference is still deemed proper.

20. Applicant's argument (2) that Pumpens' statement that foreign insertions exert a stabilizing effect on chimeric HBcΔ lacks legitimacy because it is based on unpublished results is not convincing because Pumpens' statement is published as a written record. Any published statements, suggestions, opinion, written records, etc. reflect the state of the prior art and knowledge of one of skill in the art, and can be used for assessing the obviousness of an invention at the time the invention is made.

21. In response to applicant's argument (3), Zlotnick's study is related to HBV assembly, which has provided general knowledge that would lead one of ordinary skill in the art to combine the relevant teachings of the references. Specifically, Zlotnick has studied the encapsidation and organization of a HBV pregenome by investigating the determinant of HBV capsid assembly. Zlotnick teaches that the protamine domain (residues 150-183) is required for packaging RNA and that deletion of this region results in the generation of virus capsids free of RNA and that deletion of this region results in the generation of virus capsids free of RNA encapsidation (abstract; pg. 9556, col.1; pg. 9560, col. 2).

22. Zlotnick also teaches that the addition of a single heterologous Cys at a truncated C-

terminal of HBV can stabilize the virus capsid after deletion of its protamine domain 150-183. (See Capsids assembled from Cpg. 9558, col. 6). To illustrate this, Zlotnick has created constructs Cp*149 and Cp*150 which contain HBc having a deleted C-terminal. He has replaced three native internal Cys by three Ala in the constructs Cp*149 and Cp*150, since Ala is a simplest amino acid residue and has minimal effect on the formation of higher protein structure. In addition, Zlotnick has introduced a single heterologous Cys at the truncated C-terminal of Cp*150. Zlotnick has shown that the Cp*150 construct that contained no internal Cys and had a C-terminal Cys is more stable than the Cys-free construct Cp*149, suggesting that disulfide bond formation by Cp*150 can promote capsid assemble (Results and Discussion, paragraph 1 and 2, p. 9558).

23. Thus, Zlotnick has provided the knowledge of minimal determinant of HBV capsid assembly, which is important for the art of basic and applied HBV virology, because "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). In the instant case, one of ordinary skill in the art would apply this general knowledge of HBV assembly to the construction of HBc chimer.

24. As discussed in the previous Office action, it is known in art that one of the potential problems with full-length HBc core protein molecules is that the C-terminal sequence, including the protamine region, is responsible for the packaging of nucleic acid, and, moreover, when one includes this region in a chimera one runs the risk of inadvertent transfer of endogenous nucleic acid from the host cell (See Ulrich, et al., 1998, pg. 163; cited by applicant as A108). Deletion

of protamine domain results in virus capsids free of RNA encapsidation (abstract; pg. 9556, col.1; pg. 9560, col. 2).

25. One of ordinary skill in the art would have been motivated to combine the teachings of Pumpens outlining the various uses of HBc as an epitope carrier with that of Zlotnick because it was well known that HBc chimeras with c-terminal deletions, while still capable of self-assembly, were less stable than their full-length counterparts and that by adding back amino acid residues to these c-terminal deletion one could achieve a more stable chimera, while Zlotnick teaches that the addition of a cysteine residue to an HBc c-terminal truncation results in enhanced stability.

26. One of ordinary skill in the art would have expected achieve a more stable HBc chimera with a c-terminal truncation by the addition of a cysteine residue because Zlotnick teaches that the addition of a cysteine to the c-terminal of an HBc molecule with a c-terminal truncation results in enhanced stability. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Claims 79-82 and 110-112 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thornton et al. (U.S. Patent No. 5,143,726) in view of Zlotnick et al (1997).

27. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary. The Applicant has not provided any compelling reason or evidence to overcome the rejection under 35 U.S.C. §103.

28. The rejections of claims 79-82 and 110-112 under 35 U.S.C. §103, as being unpatentable

over Thornton et al (US Patent No. 5,143,726) in view of Zlotnick et al. (1997) **are maintained**. Applicant argues that Thornton's reference does not apply for the instant claims because Thornton's construct is a full-length HBcAg, and Thornton teaches the use of an amino acid side chain for linking to saccharide, while the instant claims require a heterologous linker and that linker be placed within the region of the immunogenic loop.

29. Applicant's argument is not convincing because the heterologous linker of the instant invention, which is an amino acid residue for a conjugated epitope, is same as Thornton's, and its location in HBc molecule has been taught by Thornton. To describe the method for operatively linking individual polypeptides through an amino acid residue side chain to form an immunogenic conjugate, for example, Thornton teaches "as is well known in the art, both the HBcAg protein and polypeptide immunegen can be used in their native form or their functional group content may be modified by succinylation of lysine residues or reaction with cysteines-thiolactone" (US 5,143,726, line 13-line 45, column 10).

30. In consist with Thornton's reference, the instant claim 17 reads: "The recombinant HBc chimer protein molecule according to claim 16 wherein said heterologous linker residue for a conjugated epitope is selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue" (claim 17, also see claim 60). In the instant specification, Applicant describes "the heterologous linker for a conjugated epitope is most preferably a lysine (K) residue. Glutamic or aspartic acid, tyrosine and cysteine residues can also be used as linker residues, as can tyrosine and cysteine residues" (specification, p39). Thus, one can reasonably conclude that the heterologous linker of instant invention can be selected from the group consisting of a lysine, aspartic acid, glutamic acid, cysteine and a tyrosine residue, which can be

coupled to polypeptides through chemical reaction, such as succinylation of lysine residues or reaction with cysteines-thiolacton as taught by Thornton.

31. Furthermore, Thornton teaches a polypeptide immunegen comprising operatively linking the polypeptides through an amino acid residue side chain to "a portion of amino acid residue sequence of HBcAg from position 70 to about position 140 from the amino terminus" (Thornton, US 5,143,726, claims 3 and 5). Since the heterologous linker of the instant invention is placed at the immunedominant loop that is located between amino acids 75-85 of HBc, the immunedominant loop is covered by the Thornton's reference between position 70 to about position 140 from the amino terminus. Therefore, Thornton's reference is relevant to instant invention because Thornton has specifically taught the heterologous linkers of the instant invention.

32. Thornton does not teach the use of a C-terminal truncated HBcAg, but Zlotnick does. Zlotnick teaches a recombinant HBc molecule that does not bind nucleic acid and with enhanced stability. Zlotnick et al. teach a recombinant hepatitis B core (HBc) protein molecule (immunogenic particle) with a C-terminal cysteine as variously described above (see particularly the section relating to 102(b)). Zlotnick teaches that these molecules are capable of assembling into capsids and that they are more stable than molecules without the C-terminal cysteine residue (pg. 9558). Zotnick also indicates that these C-terminal truncations with the cysteine residue do not package RNA within their capsids.

33. One of ordinary skill in the art would have been motivated to combine the teachings of Thornton with that of Zlotnick because Zlotnick teaches that a truncated molecule loses the ability to pack endogenous nucleic acid while the addition of the C-terminal cysteine greatly

enhances the stability of the resulting truncated particles. One of ordinary skill in the art would have expected achieve a more stable HBc molecule that could present an epitope via a side-chain with a greatly diminished risk of carrying nucleic acids from the cell in which the particles were produced. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

34. The rejections of claims 79-97 and 110-115 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over (1) claims 1-46 of copending Application 10/732,862 **are withdrawn** in view of approval of a terminal disclaimer.

35. Receipt is acknowledged of papers about Inventionship issue submitted by applicant, which papers have been placed of record in the file.

36. The information disclosure statement submitted on March 28, 2005 is in compliance with the provisions of 37 CRF 1.97. Accordingly, the information disclosure statement has been considered by the examiner. An initialed and dated copy of Applicant's IDS form 1449 is attached to the instant Office action.

Remarks

37. No claim is allowed. Accordingly, **THIS ACTION IS MADE FINAL**.

A shortened statutory period for reply to this final action is set to expire THREE

MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

BP

Bo Peng, Ph.D.
June 14, 2006

JEFFREY STUCKER
PRIMARY EXAMINER